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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/641,802	08/17/2000	Istvan Boldogh	265.00240101	5387

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EXAMINER	
NICHOLS, CHRISTOPHER J	
ART UNIT	**PAPER NUMBER**
1647	20

DATE MAILED: 08/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/641,802	BOLDOGH ET AL.	
	Examiner	Art Unit	
	Christopher Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *17 August 2000* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *6 14 19* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *16* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Amendment filed 18 July 2003 (Paper No. 18) has been entered in full. Claims 16 and 17 have been added. Claims 1-17 are under examination.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. All the references cited herein have been made of record on an Information Disclosure Statement or a previous PTO-892 form.

Election/Restrictions

4. Applicant's election **with** traverse of Group 37 (Claims 1-15), in part drawn to methods of contacting cells with SEQ ID NO: 2 in Paper No. 8 (17 July 2002) is acknowledged. The *continued* traversal is on the ground(s) that: (a) claims 1-6, 9-11, 14, and 15 are linking claims, (b) the Examiner's restriction appears to be more appropriately an election of species with respect to specific sequences, and (c) request of rejoinder of Group 70 with Group 35.

5. Applicant's arguments have been fully considered but are not found to be persuasive for the following reasons. On "(a)", the Examiner does not dispute that claims 1-6, 9-11, 14, and 15 may be linking claims, however, since no allowable matter has been identified, the argument is not relevant to the current prosecution. To answer "(b)", the restriction requirement as set forth in Paper No. 7 (18 June 2002) was not an election of species pursuant to Markush Practice but was in fact, a restriction requirement between distinct and independent groups (see MPEP §803.02). On "(c)", as not allowable subject matter has been identified, no rejoinder is herein

granted. The Applicant is reminded that upon reaching allowable matter, rejoinder of groups will be considered.

Withdrawn Objections And/Or Rejections

6. The rejection of claims **1-8** as set forth at pp. 5-7 ¶11-17 of the previous Office Action (Paper No. 15, 21 March 2003) is *withdrawn in part* in view of Applicant's arguments (Paper No. 18, 18 July 2003).

Maintained Objections And/Or Rejections

7. Claims **1-17** are objected to because of the following informalities: SEQ ID NO's 1 and 3-34 are non-elected inventions pursuant to the restriction requirement 18 June 2002 (Paper No. 7) is *maintained*. As discussed above, the restriction requirement is still in effect and no rejoinder has been granted. Appropriate correction is required.

8. Claims **1-8** and **16** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for promoting neuronal cell differentiation *in vitro* with SEQ ID NO: 2, full-length colostrinin, or active analogs as put forth in claim 1, does not reasonably provide enablement for the claimed methods for promoting neuronal differentiation *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims as set forth in at pp. 5-7 ¶11-17 of the previous Office Action (Paper No. 15, 21 March 2003).

9. The Applicant traverses the rejection of claims 1-8, extended to cover newly added claim 16, on the grounds that: (a) PC12 and SH-SHY5Y cells lines are well characterized and well accepted *in vitro* model systems for the study of neuronal differentiation. The Applicant cites several journal articles to support this.

10. Applicant's arguments have been fully considered. The rejection of claims 1-8 has been amended accordingly. However, the Examiner maintains the rejection of claims 1-8 on the grounds that while PC12 and SH-SHY5Y cells lines are well characterized and well accepted *in vitro* model systems for the study of neuronal differentiation, they are not predictive of *in vivo* method. Currently the claims are broadly written and encompass methods of therapy using SEQ ID NO: 2 and its functional analogues. It is noted, however, that the amount of experimentation to practice the claimed method *in vitro* is not undue.

11. The specification as filed fails to provide any guidance for the successful use of SEQ ID NO: 2 and its functional analogues, and since resolution of the various complications in regards to targeting the effect of a protein in an organism in neuronal cell differentiation is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of formulations with known neuronal cell differentiation signs and symptoms to correlate with SEQ ID NO: 2 administration. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

12. Since the specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of using SEQ ID NO: 2 and its functional analogues in a patient. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific polypeptide or peptide fragment *in vivo* based solely on its performance *in vitro* is highly problematic (see MPEP 2164.02). Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* diagnostic assays, such a disclosure would not be considered enabling since the state of neuronal cell differentiation is highly unpredictable. The factors listed below have been considered in the analysis of enablement:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

13. In regards to the effects of colostrinin and its known analogs on cognition or neuronal cells, Popik *et al.* (29 January 2001) "Cognitive effects of Colostral-Val nonapeptide in aged rats." Behavioral Brain Research **118**(2): 201-208 teaches that Colostral-Val nonapeptide CVNP (*Val-Glu-Ser-Tyr-Pro-Leu-Phe-Pro*, 22.2% proline) shows a strong effect on the primary and secondary immune response against SRBC (T-cell dependent antigen) in mice. Also, CVNP, although less potent than full-length colostrinin, did induce production of interferon (INF) and tumor necrosis factor-α (TNF-α) in human peripheral blood leukocytes and whole blood cell cultures. It is also of note that full-length colostrinin, induces maturation and differentiation of

murine thymocytes and affects humoral and cellular immune reactions, in both *in vitro* cultures and *in vivo* (pp. 201-202).

14. When administered to aged rats Popik *et al.* teaches that CNVP is not believed to have any direct effects the process of acquisition of spatial memory (such as being a "*neuronal cell regulator*"). Indeed, CVNP and colostrinin had different effects in the studies presented by Popik *et al.* (Figures 1-5). Furthermore Popik *et al.* attribute the effects of CVNP on the rats to their immunomodulatory properties and not any direct effect on the nervous system (pp. 306-307). Taking Popik *et al.* into account, a skilled artisan would have doubt that colostrinin analogs were inducing acting as "*neuronal cell regulators*" *in vivo.*

15. On the state of the prior art, Inglot *et al.* (1996) "Colostrinine: a proline-rich polypeptide from ovine colostrums is a modest cytokine inducer in human leukocytes." Arch. Immunol. Ther. Exp. (Warsz). 44(4): 215-224 (**IDS**) teaches that colostrinin or an active analog thereof [an active nonapeptide fragment of PRP, NP (V-Q-S-Y-V-P-L-F-P), which contains 22.2% proline] induces IFN and TNF-α production in human peripheral blood mononuclear leukocytes (PBL) *in vitro* (pp. 217 Table 1; pp. 218 Table 3). In light of this evidence, a person of ordinary skill in the art would doubt that these colostrinin analogs were inducing acting as "*neuronal cell regulators*" and changing "*the cells in morphology to form neuronal cells*". Thus the claimed full scope of the invention is contrary to the teachings of the prior art to the extent of practicing the method *in vivo.*

16. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* use as exemplified in the references herein.

17. The rejection of claims 1-8 under 35 USC §112 ¶1 is maintained.

18. Claims **9-13** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as set forth in at pp. 8-10 ¶18-24 of the previous Office Action (Paper No. 15, 21 March 2003).

19. The Applicant traverses the rejection of claims 1-8 on the grounds that: (a) PC12 and SH-SHY5Y cells lines are well characterized and well accepted *in vitro* model systems and correlate with *in vivo* therapy applications, (b) the Examiner has provided no reasons for the lack of enablement, (c) the Applicant cites several journal articles concerning PC12 and SH-SHY5Y cells lines.

20. Applicant's arguments have been fully considered but are not deemed to be persuasive for the following reasons. On (a) while PC12 and SH-SHY5Y cells are an art-accepted *in vitro* model to study cell differentiation, they are not indicative of the unpredictability and obstacles to practicing the invention *in vivo*. The skilled artisan would accept cell culture experiments as clearly indicative of the therapeutic value of a peptide and its functional analogues. The claims are drawn very broadly to methods of therapy comprising promoting neuronal cell differentiation in a patient including humans (see discussion above). Further, the Applicant has not provided any examples of *in vivo* use of SEQ ID NO: 2 and its functional analogues *in vivo*. The Specification as filed only offers a prophetic example which describes an embodiment of the invention based on predicted results rather than work actually conducted or results actually

achieved. Furthermore MPEP §2164.02 states that the lack of a working example is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. This has been put forth in the previous Office Action and in the discussion above.

21. On "(b)", the Applicant is directed to the previous Office Action (and the discussion herein) wherein prior art using colostrinin and its functional analogues *in vivo* do not show any neuronal differentiation *in vivo*. Colostrinin and its functional analogues, including SEQ ID NO: 2, are known immunomodulators and Popik *et al.* attributes the effects of CVNP (a colostrinin analogue) on rats to its immunomodulatory properties and not any direct effect on the nervous system (pp. 306-307). Thus, Popik *et al.* is, in fact, a working example of administration of functional analogues of colostrinin.

22. Concerning the articles quoted by the Applicant in "(c)". While providing ample evidence for the use of PC12 and SH-SHY5Y cell lines for various in vitro purposes, none are concerned with the representation of either cell line for therapeutic applications. Further, none of the references concern the instantly claimed peptide and functional analogues thereof.

23. The rejection of claims 9-13 under 35 USC §112 ¶1 is maintained.

24. Claims **14, 15,** and **17** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention as set forth in at pp. 8-10 ¶18-24 of the previous Office Action (Paper No. 15, 21 March 2003).

25. The Applicant traverses the rejection of 14 and 15, extended to cover newly added claim 17, on the grounds that: (a) the Examiner has required in vivo animal experiments or human clinical trials, (b) the silence of WO 98/144773 is not evidence that colostrinin, its constituent peptides, and analogs will not have activity as neuronal cell regulators, (c) the teachings of the effect of colostrinin, its constituent peptides, and analogs as immunomodulatory and capable of treating damage neurons are mutually exclusive.

26. Concerning "(a)", no such requirement was set forth in the previous Office Action (see discussion above). The Applicant is reminded that WO 98/14773 demonstrates that administering colostrinin to human patients causes hyporeactivity or tolerance in the immune system, manifested by the inability to synthesize IFN and TNF-α WO 98/14773 pp. 20-21 (**IDS**). This hyporeactivity or tolerance is temporary and stops after the termination of the administration of colostrinin WO 98/14773 pp. 20-21 (**IDS**).

27. On "(b)", the Applicant and the Examiner *agree* that WO 98/144773 that said reference provides no evidence to support the claims that colostrinin, its constituent peptides, and analogs have activity as neuronal cell regulators.

28. In response to "(c)", the Examiner has cited the prior art in view of In re Wands to demonstrate the lack of support for the effects of colostrinin, its constituent peptides, and analogs as neuronal cell regulators. It is accepted that they are not mutually exclusive, but it still remains to be shown in the art or through teachings of the instant Specification that colostrinin, its constituent peptides, and analogs have activity as neuronal cell regulators.

29. More specifically, on the breath of the claims, the claims as written read on the use of SEQ ID NO: 2 and its functional analogues to revive dead tissue, resurrect deceased patients who

have died from brain failure, and repair all known and unknown causes of nonfunctional neurons. This is clearly not supported by the Specification and prior art.

30. The art also teaches that colostrinin and its active analogs have activity as cytokines and not neuronal cell regulators. For instance, Kruzel *et al.* (December 2001) "Towards and Understanding of Biological Role of Colostrinin Peptides." Journal of Molecular Neuroscience **17**(3): 379-389 discloses the identification and synthesis of 42 constituent peptide fragments of full-length colostrinin (Table1). Kruzel *et al.* also teaches that select peptide fragments induce proliferation and cytokine release (Table 3 and Table 4). Kruzel *et al.* also discloses the usefulness of using colostrinin and constituent peptides for Alzheimer's patients citing the peptide fragment's ability to induce cytokines and reduce oxidative stress but not a role as a "*neuronal cell regulator*" (pp. 388).

31. Furthermore the prior art also teaches that proline-rich polypeptide (PRP), an active analog of colostrinin is useful for treating an autoimmune disease, not neurodegeneration or any nervous system nonfunction. Zimecki *et al.* (1991) "Effect of a proline-rich polypeptide (PRP) on the development of hemolytic anemia and survival of New Zealand Black (NZB) mice." Achivum Immunologiae Et Therapiae Expermimentalis **39**: 461-467 (**IDS**) teaches that PRP (an active analog of colostrinin with 22.2% proline) induces the differentiation of immature T cells into functionally active T helper and T suppressor cells (pp. 461 and 466). Zimecki *et al.* (1991) demonstrated that administration of PRP prolonged the life span of mice with an autoimmune disease (Table 1 and 2). Thus the prior art gives the skilled artisan support for the use of colostrinin and SEQ ID NO: 2 for the treatment of immune cell nonfunction not neuronal cell nonfunction.

32. Finally, as set forth in the previous Office Action and herein maintained, the use of *in vitro* systems as support for *in vivo* methods, the *in vitro* system as presented in the instant application is not predicative of an *in vivo* method. The *in vitro* system as presented in the instant application is not an art-recognized model system for the therapy claimed.

33. The rejection of claims 14, 15, and 17 under 35 USC 112 ¶1 is maintained.

Summary

34. Claims 1-17 are hereby rejected.

35. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is 703-305-3955. The examiner can normally be reached on Monday through Friday, 8:00AM to 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on 703-308-4623. The fax phone numbers for the organization where this application or proceeding is assigned are 703-872-9306 for regular communications and 703-872-9307 for After Final communications. The fax phone numbers for the customer service center is 703-872-9305

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Elizabeth C. Kemmerer

CJN
August 8, 2003

ELIZABETH KEMMERER
PRIMARY EXAMINER